NEWBORN SCREENING News

SUMMER 2007

THE CALIFORNIA NEWBORN SCREENING PROGRAM

Upcoming Addition to Newborn Screening: Cystic Fibrosis and Biotinidase Deficiency

In accordance with Chapters 47 and 48 Statutes of 2006, commonly referred to as the 2006 Budget Act, the California Newborn Screening Program will be expanding to include Cystic Fibrosis (CF) and Biotinidase Deficiency (BD). This expansion will mean that by August 1, 2007, the over half a million babies born in California will be screened for these two disorders in addition to the current panel of metabolic, hemoglobin, and endocrine diseases.

Biotinidase Deficiency

Individuals with BD have an inactive biotinidase enzyme that cannot release biotin so it can be recycled. Biotin, a vitamin cofactor, is necessary for organic acid metabolism. Untreated BD may lead to severe metabolic decompensation in the newborn period. Affected children may exhibit seizures, hypotonia, ataxia, developmental delays, vision problems, hearing loss, skin rashes and/or other cutaneous abnormalities. If left untreated, BD can lead to mental retardation and death.

Activity of the biotinidase enzyme is measured directly using a colorimetric measurement. If the sample has no color development, confirmatory testing is indicated. A serum specimen will be sent to the state confirmatory laboratory at Stanford University.

There are two types of biotinidase deficiency, partial and profound. The California Program will be screening only for profound deficiency, since these babies require prompt treatment. National data indicates a prevalence rate of 1/83,000 for profound deficiency. This translates to about 7 profound cases per year in California. Since the expected number of cases is based on data from other states whose populations are demographically different than California, and the incidence is low and variable, the actual number of cases may vary.

Based on an analysis of about 5000 California samples, preliminary estimates of the expected positive rate is 0.02%. This should be considered tentative since it is based on such a small number.

Although the Program is screening for profound BD, some (but not all) babies with partial deficiency will be detected through screening. Newborns with positive screening results will be referred to a CCS-approved Metabolic Center. The Metabolic Center will work with the primary care provider to arrange for confirmatory testing.

For more information about BD, and copies of the provider fact sheet, please visit our website at www.dhs.ca.gov/nbs or call your local NBS Area Service Center (see list of ASCs on page 4).

Cystic Fibrosis

This summer cystic fibrosis will be added to the panel of newborn disorders that are screened for in California. The expansion follows six years of research to determine the most favorable screening method possible in California's heterogeneous population. A recent review of the benefits of newborn screening for cystic fibrosis can be found on the CDC website (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5313a1.htm).

Cystic fibrosis is an autosomal recessive disease requiring a mutation on each of the two copies of chromosome 7 inherited from our parents. CF can cause damage to a number of different body organs, including the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract.

One or more of the following cystic fibrosis symptoms are typical in the first few months of life: slow growth and failure to thrive; recurrent respiratory infections, including respiratory syncytial virus (RSV); salty sweat; malnutrition and frequent runny stools. In 15-20% of cases, meconium ileus (a congenital intestinal obstruction by thickened viscous meconium) will be present in the first days of life. In hot environments, persons with cystic

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fibrosis can dehydrate and develop life-threatening electrolyte imbalance.

Cystic fibrosis prevalence rates at birth differ widely across race/ethnicity groups (Exhibit 1), as do the types of mutations that cause the disease. To date, over 1400 different CFTR mutations have been identified. Around 92 cases of cystic fibrosis are expected out of about 540,000 births per year in California.

Exhibit 1:
Cystic fibrosis prevalence rates and expected annual births with cystic fibrosis by race/ethnicity.

Race/Ethnicity	CF Prevalence Rate	Number of Births
Non-Hispanic Whites	1/3,000 births	59
Hispanics	1/9,000 births	30
Non-Hispanic Blacks	1/15,000 births	2
Asians and Others	1/45,000 births	1
Total	**1/5,876 births**	**92**

In California, a four-step screening model for cystic fibrosis will be implemented as described below. (A flow chart with expected annual numbers can be found in Exhibit 2.) All newborn blood spots are tested for immunoreactive trypsinogen (IRT) at the regional Neonatal and Prenatal Screening (NAPS) Laboratory (Step One). Newborns with values in the top 2.2% of the IRT distribution (n~11,844 per year) will have their blood spots tested at Stanford University for the presence of 38 different CFTR mutations (Step Two). Newborns with low IRT values or zero mutations are deemed to be screen negative for cystic fibrosis (n~539,882). Those with one mutation found (n~876 per year) will have one of their existing filter paper blood spots sent to Ambry Genetics for more sophisticated testing using DNA sequencing methods capable of detecting over 98% of all CFTR mutations (Step Three). Newborns with two or more mutations identified are screen positive for cystic fibrosis (n~104 per year) and, in conjunction with the newborn's primary care provider, will be referred to a Cystic Fibrosis Special Care Center for a diagnostic work up and sweat chloride test (Step Four).

The parents of newborns with only one mutation identified (about 900 per year) will be sent a letter informing them that their baby is a carrier (as is one or both of the parents) and will be offered genetic counseling by telephone.

Annually, 92% (n~85) of the expected 92 newborns with cystic fibrosis will be detected by the Newborn Screening Program: 69 cases at around seven days of age (Step Two), and 16 cases at around one month of age (Step Three). Maternity hospitals and primary care physicians will be sent an initial results mailer after Step One (for those newborns with a negative IRT result) or Step Two (for those with a positive IRT result) but with no mutations identified.

For approximately 876 newborns whose blood spots were sent on for Step Three testing, hospitals and primary care physicians will receive a preliminary report of a single CFTR mutation, stating that further cystic fibrosis testing is in process. Because over 98% of these newborns will be carriers and not have cystic fibrosis, it is important for primary care physicians to wait to refer newborns for diagnostic sweat testing until after Step Three results are received, with three exceptions:

- The newborn has clinical symptoms of cystic fibrosis
- There is a family history of cystic fibrosis, or
- Both parents are known carriers of a CFTR mutation.

After Step Three, a DNA Sequencing Results Mailer will be sent with final mutation results.

The California CF newborn screening model has been designed to detect at least 90% of CF cases in California's Hispanic, Black and White populations. Because no newborn screening model for cystic fibrosis can detect 100% of the cases while minimizing false positives, primary care providers need to remain vigilant for signs and symptoms of cystic fibrosis regardless of newborn screening results. Reporting to GDB will be mandatory for all newly diagnosed cases of cystic fibrosis in California, whether or not screened by the newborn screening program.

For additional information about cystic fibrosis newborn screening, please visit our website at www.dhs.ca.gov/nbs or call your local NBS Area Service Center. ■

Additional Information for Health Care Providers and Families

The Program booklet called *Important Information for Parents about the Newborn Screening Test* is being updated to reflect the upcoming expansion. A note indicating when to start using them will be included inside the boxes containing the booklet. We will be requesting you destroy/recycle all copies of the old version of the booklet and only use the updated version once expansion begins.

Many other educational materials are being developed in preparation for expansion, including fact sheets for providers and booklets for parents of babies diagnosed with CF or biotinidase deficiency. These and other NBS educational materials can be ordered by calling (510) 412-1542. They will also be available from the NBS website, www.dhs.ca.gov/nbs. Recent Program newsletters and letters to hospitals and providers are also posted on the website.

Referral for Diagnostic Evaluation and Treatment

All newborns identified with a disorder through the NBS Program should have access to a diagnostic evaluation through a CCS-approved Special Care Center (SCC). (See list on last page of this newsletter.) Specialists at the SCC will work closely with the primary care provider in determining appropriate follow-up and in the development of a treatment plan when necessary. When a disorder is confirmed, the NBS Program strongly recommends that newborns receive ongoing care at a SCC where a multi-disciplinary team (physicians, dietician, nurse, social worker, genetic counselor) can provide a comprehensive approach to assisting the family.

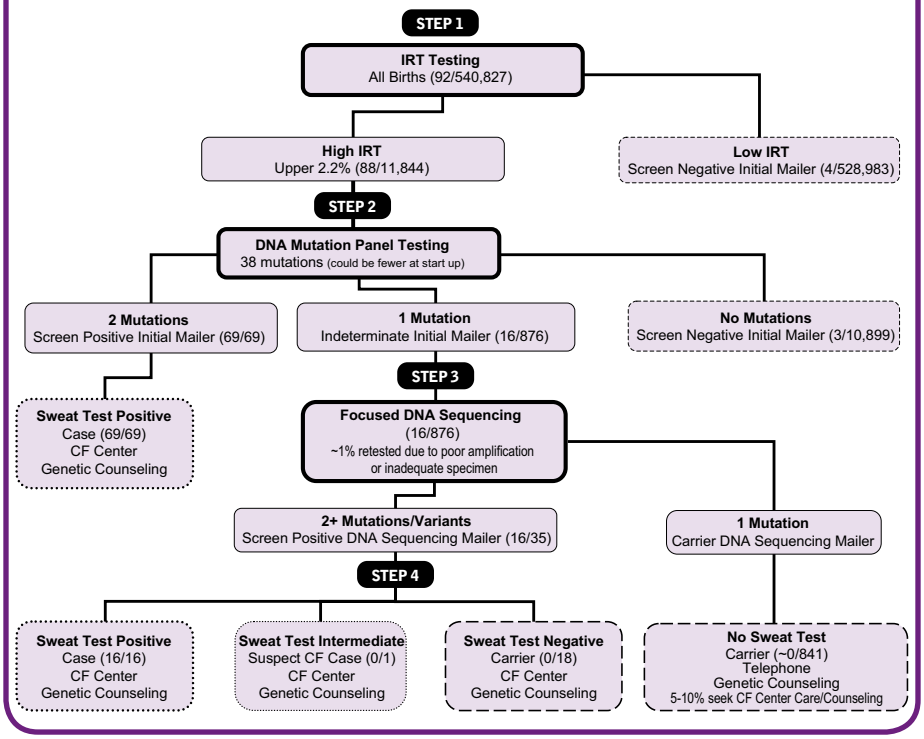
Who Will Pay for the Diagnostic Evaluation and Treatment if Needed?

All newborns referred to a CCS-approved SCC by the California Newborn Screening Program are eligible for a diagnostic evaluation through the SCC regardless of income. The ASC will work with the primary care provider in determining which SCC to refer the baby to based upon location, insurance plan coverage and provider preference. Because the disorders screened for by the NBS Program require immediate follow-up, the CCS program has developed an expedited authorization process to assure a prompt initial diagnostic evaluation at a SCC.

Parents will be asked to complete an application form to determine eligibility for CCS payment for the diagnostic evaluation. Most health insurance and health maintenance organizations (HMOs) provide at least some coverage for the diagnostic evaluation and any necessary treatment. If a baby has health insurance the SCC will bill the health insurance company or HMO for the services. Infants who have Medi-Cal full scope, no share of cost, or Healthy Families subscribers will be authorized by CCS for diagnostic and treatment services and parents will not need to pay anything for services. If parents do not have health insurance, or their insurance only covers partial payment, the infant may be eligible for the CCS program. Eligibility for coverage of treatment costs through the CCS program is based on having a CCS eligible medical condition, and meeting CCS financial and residential eligibility criteria. For more information on the CCS program visit their website at: http://www.dhs.ca.gov/pcfh/cms/ccs/. For a list of SCCs see page 4 of this newsletter. ■

EXHIBIT 2:

California CF Newborn Screening Model with Annual Numbers (Cases/Others)



Limitations of the Newborn Screening Program

Due to biological variability of newborns and differences in detection rates for the various disorders in the newborn period, the Newborn Screening Program will not identify all newborns with these conditions. While a positive screening result identifies newborns at an increased risk to justify a diagnostic work-up, a negative screening result does not rule out the possibility of a disorder. Health care providers should remain watchful for any signs or symptoms of these disorders in their patients. **A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable health care provider.** ■

California Children's Services Approved Special Care Centers

including Metabolic, Endocrine, Sickle Cell Disease/Hemoglobin and Cystic Fibrosis*

Cedars-Sinai Medical Center
Los Angeles, CA 90048
Metabolic – (310) 423-9914
SCD/Hb. – (310) 423-4423

Children's Hospital & Research Center at Oakland
Oakland, CA 94609
Metabolic – (510) 428-3550
Endocrine – (510) 428-3654
SCD/Hb. – (510) 428-3651
Cystic Fibrosis – (510) 428-3305

Children's Hospital Central California
Madera, CA 93638
Metabolic – (559) 353-6400
Endocrine – (559) 353-8700
SCD/Hb. – (559) 353-5461
Cystic Fibrosis – (559) 353-5587

Childrens Hospital of Los Angeles
Los Angeles, CA 90027
Metabolic – (323) 660-2450
Endocrine – (323) 660-2450
SCD/Hb. – (323) 660-2450
Cystic Fibrosis – (323) 669-4539

Children's Hospital of Orange County
Orange, CA 92868
Metabolic – (714) 532-8852
Endocrine – (714) 532-8634
SCD/Hb. – (714) 532-8459
Cystic Fibrosis – (714) 532-8620

Rady's Children's Hospital, San Diego
San Diego, CA 92123
Metabolic – (619) 543-7800
Endocrine – (858) 966-4032
SCD/Hb. – (858) 966-5811
Cystic Fibrosis – (858) 966-6790

City of Hope Medical Center
Duarte, CA 91010
SCD/Hb. – (626) 256-4673 ext. 62913

Harbor/UCLA Medical Center
Torrance, CA 90509
Metabolic – (310) 222-3756
Endocrine – (310) 222-2394
SCD/Hb. – (310) 222-2394

Kaiser Permanente No. California
Oakland, CA 94611
Metabolic – (510) 752-7703
SCD/Hb. – (510) 752-6192
Cystic Fibrosis – (510) 752-6596**

Kaiser Permanente So. California
Los Angeles, CA 90033
Metabolic – (323) 783-6970
SCD/Hb. – (800) 734-5155
Cystic Fibrosis – (818) 375-2909**

Loma Linda University
Loma Linda, CA 92354
Endocrine – (909) 558-2827
SCD/Hb. – (909) 558-2617
Cystic Fibrosis – (909) 558-2301

Los Angeles County/USC
Medical Center
Los Angeles, CA 90033
Metabolic – (323) 226-3816
SCD/Hb. – (323) 226-3853

Lucile Salter Packard Children's Hospital at Stanford
Palo Alto, CA 94301
Metabolic – (650) 723-6858
Endocrine – (650) 723-5791
SCD/Hb. – (650) 725-1072
Cystic Fibrosis – (650) 723-5191

Miller Children's at Long Beach Memorial Medical Center
Long Beach, CA 90801
Endocrine – (562) 933-8562
SCD/Hb. – (562) 492-1062
Cystic Fibrosis – (562) 933-8567

Pediatric Diagnostic Center Ventura County Medical Center
Ventura, CA 93003
Cystic Fibrosis – (805) 641-4490

Pediatric Specialties Clinic
Walnut Creek, CA 94598
Cystic Fibrosis – (925) 280-8131

Saint Agnes Medical Center
Fresno, CA 93720
SCD/Hb. – (209) 449-5121

Santa Clara Valley Medical Center
San Jose, CA 95128
Endocrine – (408) 885-5405

Sutter Memorial Hospital
Sacramento, CA 95819
Metabolic – (916) 733-6023
Endocrine – (916) 733-6006
SCD/Hb. – (916) 733-1757
Cystic Fibrosis – (916) 453-1454

UC Davis Medical Center
Sacramento, CA 95817
Metabolic – (916) 734-3112
Endocrine – (916) 734-3112
SCD/Hb. – (916) 734-2781
Cystic Fibrosis – (916) 734-3189

UC San Francisco Medical Center
San Francisco, CA 94143
Metabolic – (415) 476-2757
Endocrine – (415) 476-1016
SCD/Hb. – (415) 502-8034
Cystic Fibrosis – (415) 476-2072

UC Irvine Medical Center
Orange, CA 92868
Metabolic – (714) 456-8513
SCD/Hb. – (714) 456-5680

UC Los Angeles Medical Center
Los Angeles, CA 90095
Metabolic – (310) 206-6581
Endocrine – (310) 825-6244
SCD/Hb. – (310) 825-6708

Newborn Screening Area Service Centers (NBS-ASCs)

Stanford University
(650) 812-0353

Children's Hospital Central CA
(559) 353-6416

UCLA Medical Center
(310) 826-4458

Harbor/UCLA Medical Center
(310) 222-3751

San Diego Region
(800) 793-1313

Kaiser Permanente, Northern CA
(510) 752-6192

Kaiser Permanente, Southern CA
(626) 564-3322

*CF Centers must also be Cystic Fibrosis Foundation Accredited. / **Not CCS approved - Kaiser members only

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